SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICALPRODUCT

Lovarem 20 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20mg Lovastatin

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lovarem is used as an adjunct to dietary therapy to decrease elevated serum total and LDL-cholesterol concentrations in the treatment of primary types IIa and IIb hyperlipoproteinaemia (primary hypercholesterolaemia). The drug also is used to slow the progression of coronary atherosclerosis in patients with coronary heart disease (CHD) as part of a treatment strategy to lower total and LDL-cholesterol concentrations to target levels.

Nondrug therapies and measures specific for the type of hyperlipoproteinaemia are the initial treatments of choice, including dietary management (e.g., restriction of total and saturated fat and cholesterol intake), weight control, an appropriate program of physical activity, and management of potentially contributory disease (e.g., hypothyroidism). Drug therapy is not a substitute for but an adjunct to these nondrug therapies and measures, which should be continued when drug therapy is initiated.

4.2 Posology and method of administration

The usual initial dosage of Lovarem in adults is 20 mg daily given with the evening meal. Dosage should be increased at intervals of no less than 4 weeks until the desired effect on lipoprotein concentrations is observed or a maximum dosage of 80 mg daily is reached; reduction of Lovarem dosage should be considered in patients whose serum cholesterol concentrations fall below the desired target range.

The usual adult maintenance dosage of Lovarem is 10-80 mg daily given in single or 2 divided doses.

Because of an increased risk of myopathy during concomitant therapy, it is recommended that patients receiving immunosuppressive drugs such as cyclosporine with Lovarem should

receive an initial dosage of 10 mg daily; titration to higher Lovarem dosages should be done with caution and should not exceed 20 mg daily.

If lovastatin is used in combination with fibrates or niacin, the dosage of lovastatin should not exceed 20mg daily.

Dosage in renal and hepatic impairment: Although lovastatin is only minimally excreted in urine, the drug should be administered with caution in patients with severe renal impairment (creatine clearance less than 30ml/min); dosage increase above 20mg daily should be carefully considered, and if deemed necessary implemented with extreme caution.

Patients with hepatic dysfunction, lovastatin should be used with caution in patients who consume substantial amounts of alcohol and or have history of liver disease, and such patients should be monitored closely while receiving lovastatin therapy. Lovastatin should not be used in patients with active liver disease or unexplained persistent elevations in serum aminotransferase concentrations.
Dosage of Lovarem should be individualized according to the recommended goal of therapy and the patient's response. It is recommended that patients requiring reductions in LDL-cholesterol of 20% or greater to achieve their goal should be started on a Lovarem dosage of 20 mg daily; a dosage of 10 mg daily may be considered for patients requiring smaller reductions in LDL-cholesterol concentration.

Dosage of Lovarem must be carefully adjusted according to individual requirements and response. Serum lipoprotein concentrations should be determined periodically during Lovarem therapy.

Children: Safety and efficacy of lovastatin in children younger than 18 years of age have not been established.

4.3 Contraindications

A. Pregnancy and lactation
B. Active liver disease
C. Unexplained persistent elevations of serum transaminases
D. Hypersensitivity to lovastatin or any of its components

4.4 Special warnings and precautions for use

- Heavy alcohol use
- History of liver disease
- Hepatic effects:

It is recommended that transaminase tests be performed before treatment begins and periodically thereafter, particularly in patients who have abnormal liver functions tests and/or consume substantial quantities of alcohol and in patients in whom the dose is increased to 40mg/day or more.

Should serum transaminase levels rise to more than three times the ULN, the potential risk of continuing Lovarem should be weighted against the anticipated benefits. Transaminase

measurements should be repeated promptly; if these elevations are persistent progressive, the drug should be discontinued.

As with other lipid-lowering agents, moderate (less than three times the ULN) elevations of serum transaminases have been reported during therapy with Lovarem. These changes appeared soon after initiation of therapy with Lovarem. were usually transient, and were not accompanied by any symptoms; interruption of treatment was not required.

The drug should be used with caution in patients with a past history of liver disease. Active liver diseases is a contraindication to the use of Lovarem.

- Myopathy caused by drug interactions: the incidence and severity of myopathy are increased by concomitant administration of HMG-CoA reductase inhibitors with drugs that can cause myopathy when given alone, such as gemfibrozil and other fibrates, and lipid-lowering doses (1g/day) of niacin (nicotinic acid).

  In addition, the risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Lovastatin and other HMG-CoA reductase inhibitors are metabolized by the cytochrome P450 isoform 3A4. Certain drugs that have a significant inhibitory effect at therapeutic doses on this metabolic pathway can substantially raise the plasma levels of HMG-CoA reductase inhibitors and thus increase the risk of myopathy. Theses include cyclosporine, the tetralol-class calcium channel blocker mibefradil, itraconazole, ketoconazole and other antifungal azoles, the macrolide antibiotics erythromycin, and clarithromycin, and the antidepressant nefazodone.

  There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

Reducing the risk of myopathy:

1. General measures:

Patients starting therapy with lovastatin should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness or weakness. A CK level above 10X ULN in a patient with unexplained muscle symptoms indicates myopathy. Lovastatin therapy should be discontinued if myopathy is diagnosed or suspected. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved.
Of the patients with rhabdomyolysis, many had complicated medical histories. Some had pre-existing renal insufficiency, usually as a consequence of long-standing diabetes. In such patients, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with lovastatin should be stopped a few days before elective major surgery and when any major acute medical or surgical condition supervenes.

2. Measures to reduce the risk of myopathy caused by drug interactions (see above).

Physicians contemplating combined therapy with lovastatin and any of the interacting drugs should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic

CK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

The combined use of lovastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. Combination of fibrates or niacin with low doses of lovastatin have been used without myopathy insmall, short-term clinical trials with careful monitoring. Addition of these drugs to HMG-CoA reductase inhibitors typically provides little additional reduction in LDL cholesterol, but further reductions of triglycerides and further increases in HDL cholesterol may be obtained. If one of these drugs must be used with lovastatin, clinical experience suggests that the risk of myopathy is less with niacin than with the fibrates.

In patients taking concomitant cyclosporine, fibrates or niacin, the dose of lovastatin should generally not exceed 20mg, as the risk of myopathy increases substantially at higher doses. Interruption of lovastatin therapy during a course of treatment with a systemic antifungal azole or a macrolide antibiotic should be considered. Concomitant use with other medicines labelled as having a potent inhibitory on cytochrome P450 3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

- Ophthalmic evaluations: In the absence of any drug therapy, an increase in the prevalence of lens opacities with time is expected as a result of aging. Long term data from clinical trials do not indicate an adverse effect of lovastatin on the human lens.

- Interstitial lung disease: Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Diabetes Mellitus
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where normal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30Kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Lovarem must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.
Statin therapy may be re-introduced seven days after the last dose of fusidic acid.
In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of Lovarem and fusidic acid should only be considered on a case by case basis and under close medical supervision.

4.5 Interaction with other medicinal products and other forms of interaction

The risk of developing myopathy is increased if lovastatin is administered concomitantly with cyclosporine, danazol, erythromycin, mibefradil, itraconazole, ketoconazole, clarithromycin, nefazodone, verapamil, fibrates or niacin. Antilipaemic doses of niacin, vitamin B3 may also increase this risk although in some cases lovastatin has been used concomitantly with niacin safely for long periods. One case is noted of a patient who developed rhabdomyolysis when itraconazole was added to a stable regimen of lovastatin and niacin. In a small, double-blind study in healthy volunteers, lovastatin mean peak concentrations and lovastatin AUC increased by more than 20-fold when subjects were pre-treated with itraconazole. Concurrent use of lovastatin with any of these drugs may be associated with an increased risk of developing rhabdomyolysis and acute renal failure. Any patient receiving such combined therapy should be carefully monitored for myopathy or rhabdomyolysis. Serum concentrations of CPK can rise to 200,000 or higher but correlate poorly with symptoms. Myopathy or myositis can reverse if therapy is discontinued.
Intake of ethanol should be avoided or minimized during lovastatin therapy to reduce the risk of hepatic injury.

Hypoprothrombinaemia and clinical bleeding have been documented when lovastatin was added to a stabilized regimen of warfarin therapy. In patients who are receiving warfarin and who also require therapy with a HMG-CoA-reductase inhibitor, lovastatin should be avoided. It appears that pravastatin may not interact with warfarin, however some other but HMG-CoA-reductase inhibitors (e.g., fluvastatin, simvastatin) may also potentiate warfarin.

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.
If treatment with systemic fusidic acid is necessary, Lovarem treatment should be discontinued throughout the duration of the fusidic acid treatment. Also see section 4.4

Drug/Laboratory Test Interferences:
Marked persistent increases of serum transaminases have been noted.

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9 percent and probucol, 2 percent. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported.

Grapefruit juice contains one or more ingredients inhibiting cytochrome P450 3A4 and may therefore increase the plasma concentrations of drugs metabolasied via the cytochrome P450 3A4. Concomitant intake of grapefruit juice and lovastatin should be avoided.

The risk of myopathy or rhabdomyolysis is increased when lovastatin is given concomitantly with amiodarone. In an ongoing clinical trial concomitant treatment with 80mg lovastatin per day and amiodarone resulted in myopathy or rhabdomyolysis in 6% of these patients.

4.6 Fertility, pregnancy and lactation

Pregnancy
If antilipaemic drugs are considered necessary, however, lovastatin should not be used, since the drug has been shown to be teratogenic in animals and suppression of cholesterol biosynthesis could cause foetal toxicity.
Therefore, lovastatin is contra-indicated in such women.

Lactation
It is not known whether lovastatin is distributed into human milk; however, the drug is distributed into the milk of rats. Because of the potential for serious side-effects from lovastatin in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

4.7 Effects on ability to drive and use machines

Lovarem is unlikely to affect the ability to drive or operate machinery.

4.8 Undesirable effects

Lovastatin was extremely well tolerated in controlled clinical trials. Side-effects tend to be transient and mild.

Musculoskeletal disorders:

Toxicity to the skeletal muscle occurs infrequently but can be a serious side-effect to lovastatin therapy. Asymptomatic elevations of CPK occur in approximately 11% of patients, however, more serious manifestations, such as rhabdomyolysis, can also occur. Myalgia (muscle aches or cramps), fever, tiredness, or myasthenia occurs in approximately 1-3% of patients, and myopathy occurs in approximately 1%, although the risk is greater if lovastatin is administered with gemfibrozil, lipid-lowering doses of nicotinic acid, cyclosporine or other immunosuppressive agents. This toxicity appears to be reversible after discontinuation of therapy.

Frequency not known: Immune-mediated necrotizing myopathy (see section 4.4)

Gastrointestinal side-effects occur with lovastatin use but are usually mild. They include nausea/vomiting, dyspepsia, constipation or diarrhoea, flatulence, and abdominal pain.

Lovastatin therapy can cause elevated hepatic enzymes. Persistent elevations of serum transaminases have been reported. Enzyme concentrations will decrease to pre-treatment concentrations after discontinuation of lovastatin. These elevations were not associated with jaundice or other signs or symptoms of hepatotoxicity. Hepatitis, cholestasis with jaundice, anorexia, and pancreatitis have been reported during therapy with other HMG-CoA reductase inhibitors, but a causal relationship has not been established with these agents.
Headache is the most common nervous system effect from lovastatin. Dizziness has also been reported.

Allergic reactions can occur with lovastatin therapy such as rash and pruritus. Rashes can vary in severity from urticaria or purpura to toxic epidermal necrolysis or Stevens-Johnson syndrome.

Cataracts have been reported with lovastatin use, usually occurring after many months of therapy.

Lovastatin's other reported side-effects include impotence and insomnia.

The following adverse events have been reported with some statins:
- Memory loss
- Sexual dysfunction [where this is not already listed]
- Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI>30kg/m2, raised triglycerides, history of hypertension).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product isimportant. It allows continued monitoring of the benefit/risk balance of the medicinal product.Healthcare professionals are asked to report any suspected adverse reactions via the nationalreporting system.

4.9 Overdose

A few cases of accidental overdosage have been reported; no patients had any spec*i*fic symptoms and all patients recovered without sequel. The maximum dose taken was 5-6 g.
Until further experience is obtained, no specific treatment of overdosage with lovastatin can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG CoA Reductase Inhibitors
ATC Code: C10AA02 (Lovastatin)

Lovastatin represents the first of a new class of lipid-lowering agents, the HMG-CoA reductase inhibitors, which are indicated for the treatment of primary hypercholesterolaemia. Lovastatin was also the first HMG-CoA reductase inhibitor acknowledged to slow coronary atherosclerosis. Its indications were expanded to include slowing the progression of coronary atherosclerosis.

Lovastatin is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyses the conversion of HMG-CoA to mevalonate.

5.2 Pharmacokinetic properties

Lovastatin is a prodrug with little or no inherent activity but is hydrolysed in vivo to mevinolinic acid. Mevinolinic acid, one of lovastatin's several active metabolites, is structurally similar to HMG-CoA (hydroxymethylglutaryl CoA). Once hydrolysed, lovastatin competes with HMG-CoA for HMG-CoA reductase, a hepatic microsomal enzyme. Interference with the activity of this enzyme reduces the quantity of mevalonic acid, a precursor of cholesterol. This process occurs within the hepatocyte and is one of two mechanisms that generate cholesterol. Cholesterol also can be taken up from LDL by endocytosis. Since de novo synthesis of cholesterol is impaired by lovastatin, the second mechanism is augmented. Thus, lovastatin also enhances clearance of LDL. Lovastatin exerts its effects mainly on total cholesterol and LDL, with minor effects seen on HDL and triglycerides.

Lovastatin is administered orally. It is incompletely absorbed from the gastrointestinal tract and undergoes extensive first-pass extraction in the liver. Lovastatin was purposely developed as a prodrug to concentrate active drug in the liver during first-pass circulation. Because less drug reaches the systemic circulation, fewer side-effects are believed to occur. Roughly 5% of active drug reaches the systemic circulation. The presence of food in the gastrointestinal tract enhances oral absorption. Diurnal variation in the activity of the enzyme has been documented; single daily doses are most effective if given in the evening.
Lovastatin is highly bound to plasma proteins. Lovastatin crosses the blood-brain barrier and the placental barrier, and may also be distributed into human milk. Although no data exist regarding its use in pregnant women, lovastatin, in high doses, has produced foetal abnormalities in animal models.

As mentioned above, lovastatin is a prodrug that is hydrolysed to mevinolinic acid and several other active derivatives. The plasma half-life of mevinolinic acid is about 1.1-1.7 hours. Following a single dose to adults with hypercholesterolaemia, 83% is excreted in the faeces as both active and inactive metabolites.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, Butylated Hydroxyanisole, Povidone, Microcrystalline Cellulose, Pregelatinised Starch, Magnesium Stearate, Indigo Carmine E.132.

6.2 Incompatibilities

None known.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Lovarem tablets should be stored below 25^{o}C, protected from light and moisture.

6.5 Nature and contents of container

Retail packs of 30 (3 x 10) and 60 (6 x 10) tablets
Hospital packs containing 30 and 1000 tablets in PP/PE containers

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

Remedica Ltd
Aharnon Str.,Limassol Industrial Estate
3056 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

06222/07663/REN/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of latest renewal: Jul 24, 2021

10. DATE OF REVISION OF THE TEXT

06/07/2023